Recent advances in cerebrospinal fluid biomarkers for the detection of preclinical Alzheimer's disease

Kulic, Luka ; Unschuld, Paul G

Abstract: PURPOSE OF REVIEW: The concept of preclinical Alzheimer's disease has emerged to describe the long 'silent' phase of the disease when significant pathophysiological changes occur in the brain but clinical symptoms are not yet manifest. In this review, a summary of the recent advances in cerebrospinal fluid (CSF) biomarker-based diagnostics of preclinical Alzheimer's disease will be presented. RECENT FINDINGS: The association between core CSF biomarkers of Alzheimer's disease and between CSF and neuroimaging markers has been a major focus of various recently published studies in cognitively healthy individuals. Longitudinal results from several research groups suggest that CSF A 42 is altered early in preclinical Alzheimer's disease, even preceding changes on amyloid PET imaging. In line with the proposed NIA-AA criteria, elevated tau levels and/or A /tau interactions appear to be a prerequisite for neurodegeneration and future cognitive decline. Novel candidate CSF markers, including markers of neuronal and synaptic injury as well as neuroinflammation, may complement CSF-based diagnostics in preclinical Alzheimer's disease. SUMMARY: Further longitudinal research is necessary to delineate the temporal changes of core and candidate CSF biomarkers in preclinical Alzheimer's disease and to investigate their association with established and emerging neuroimaging markers as well as with comorbidities and other risk factors for age-related cognitive decline.

DOI: https://doi.org/10.1097/WCO.0000000000000399

REVIEW

OPEN

Recent advances in cerebrospinal fluid biomarkers for the detection of preclinical Alzheimer's disease

Luka Kulic[a,b,c,d] *and Paul G. Unschuld*[a,b,c]

Purpose of review
The concept of preclinical Alzheimer's disease has emerged to describe the long 'silent' phase of the disease when significant pathophysiological changes occur in the brain but clinical symptoms are not yet manifest. In this review, a summary of the recent advances in cerebrospinal fluid (CSF) biomarker-based diagnostics of preclinical Alzheimer's disease will be presented.

Recent findings
The association between core CSF biomarkers of Alzheimer's disease and between CSF and neuroimaging markers has been a major focus of various recently published studies in cognitively healthy individuals. Longitudinal results from several research groups suggest that CSF Aβ42 is altered early in preclinical Alzheimer's disease, even preceding changes on amyloid PET imaging. In line with the proposed NIA-AA criteria, elevated tau levels and/or Aβ/tau interactions appear to be a prerequisite for neurodegeneration and future cognitive decline. Novel candidate CSF markers, including markers of neuronal and synaptic injury as well as neuroinflammation, may complement CSF-based diagnostics in preclinical Alzheimer's disease.

Summary
Further longitudinal research is necessary to delineate the temporal changes of core and candidate CSF biomarkers in preclinical Alzheimer's disease and to investigate their association with established and emerging neuroimaging markers as well as with comorbidities and other risk factors for age-related cognitive decline.

Keywords
biomarker, cerebrospinal fluid, cognitive decline, neuroimaging, preclinical Alzheimer's disease

INTRODUCTION

Alzheimer's disease is the most frequent cause of age-related cognitive and functional decline and a growing socioeconomic challenge for healthcare systems of the 21st century worldwide [1]. By the time cognitive symptoms are traditionally diagnosed, significant neurodegenerative changes are already detectable in the brain and opportunities for causal disease-modifying therapeutic approaches are limited. Alzheimer's disease-related pathophysiological changes can be detected as early as 10–20 years before overt cognitive impairment [2]. The detection of these changes as biomarkers by neuroimaging techniques and/or by biochemical assays in the cerebrospinal fluid (CSF) has led to a conceptual shift in the field of early Alzheimer's disease diagnostics. The new diagnostic framework for preclinical Alzheimer's disease comprises biomarker-based research criteria developed by the workgroups of the National Institute on Aging – Alzheimer's Association (NIA-AA) [3] and those proposed by the International Working Group (IWG-2) [4]. A special focus of the NIA-AA criteria is laid on the early preclinical disease stages and the assumption that Alzheimer's disease can be regarded as a continuum ranging from normal cognition without evidence of Alzheimer's disease biomarker abnormalities to full-blown pathology including neuronal injury and cognitive decline [3,5▪▪]. As such, the NIA-AA criteria are closely

[a]Institute for Regenerative Medicine, [b]Clinic for Psychogeriatric Medicine, [c]Neuroscience Center Zurich (ZNZ) and [d]Zurich Center for Integrative Human Physiology (ZIHP), University of Zurich, Zurich, Switzerland

Correspondence to Dr Luka Kulic, Institute for Regenerative Medicine - IREM, University of Zurich, Wagistrasse 12, 8952 Schlieren, Switzerland.
Tel: +41 44 634 8848; fax: +41 44 634 8874;
e-mail: luka.kulic@irem.uzh.ch

Curr Opin Neurol 2016, 29:749–755

DOI:10.1097/WCO.0000000000000399

KEY POINTS

- Longitudinal results suggest that CSF Aβ42 is altered early in preclinical Alzheimer's disease.
- Elevated CSF tau levels and/or CSF Aβ/tau interactions appear to be a prerequisite for neurodegeneration and future cognitive decline.
- Novel candidate CSF markers, including markers of neuronal and synaptic injury as well as neuroinflammation, may complement CSF-based diagnostics in preclinical Alzheimer's disease.

centered on the amyloid cascade hypothesis [6] and the model proposed by Jack *et al.* suggesting an ordered fashion of temporal biomarker changes during preclinical and clinical disease progression [7,8]. Isolated amyloidosis (represented by reduced CSF Aβ42 and/or by positive amyloid PET) has been defined as the earliest stage of preclinical Alzheimer's disease (stage 1) according to current NIA-AA criteria [3]. Consecutive stage 2 is characterized by additional evidence of neuronal injury and/or neurodegeneration (as revealed by elevated CSF tau/p-tau, Alzheimer's disease-related hypometabolism on [^{18}F]FDG PET and/or atrophy on MRI) [3]. Lastly, a preclinical Alzheimer's disease stage 3 has been defined to describe individuals with subtle cognitive decline in addition to positive Aβ and neuronal injury/neurodegeneration biomarkers [3]. The NIA-AA staging criteria of preclinical Alzheimer's disease are based on several hypothetical assumptions, which have recently been supported or challenged by different groups, for example, the assumption that Alzheimer's disease biomarkers follow an invariable sequence of temporal changes or that certain CSF and imaging markers may be treated as if they were interchangeable [9].

In this review, a summary of the recent advances in CSF biomarker-based detection of preclinical Alzheimer's disease will be presented. A special focus will be laid on the relationship between CSF Alzheimer's disease biomarkers and neuroimaging markers and on the temporal sequence of biomarker changes during preclinical disease progression.

RELATIONSHIP BETWEEN CORE CEREBROSPINAL FLUID BIOMARKERS AND IMAGING MARKERS OF NEURODEGENERATION IN PRECLINICAL ALZHEIMER'S DISEASE

The association between the core CSF Alzheimer's disease biomarkers Aβ42, tau, and p-tau and imaging measures of neuronal injury has recently been addressed by several authors both in cross-sectional and in longitudinal studies.

Vos *et al.* [10▪] classified 212 cognitively healthy individuals according to the NIA-AA criteria and found a surprisingly low concordance (<60%) between imaging (hippocampal volume) and CSF (tau/p-tau) measures, thereby highlighting the need for further refinement and investigation into the relationship between CSF and imaging markers of neurodegeneration.

In a cross-sectional study including 188 cognitively healthy individuals, Wang *et al.* [11▪] investigated the association between neurodegeneration measured by structural MRI and the core CSF biomarkers Aβ42 and tau. The authors found that CSF Aβ42 and tau were linked to spatially distinct patterns of atrophy. Although reduced Aβ42 was associated with isolated hippocampal atrophy, elevated tau levels were related to thinning in several Alzheimer's disease-relevant cortical brain regions [11▪]. Notably, the CSF Aβ42 status had no significant influence on the association between tau and cortical atrophy in this study, suggesting the existence of both Aβ-independent and Aβ-dependent pathways of neurodegeneration in preclinical Alzheimer's disease [11▪].

In another cross-sectional study with 145 cognitively intact individuals Fortea *et al.* [12▪] analyzed the interaction between CSF Aβ42 and p-tau across the whole cortical mantle. In contrast to Wang *et al.* the authors observed that tau modified the effects of Aβ on cortical thickness in various cortical regions and vice versa. Interestingly, the presence of Aβ (measured by decreased CSF Aβ42) in the absence of p-tau was associated with cortical thickening, for example explained by increased amyloid-related inflammatory changes, while in the presence of tau these effects were reversed towards neurodegeneration and cortical thinning in individuals who were positive both for Aβ and for p-tau [12▪].

The usefulness of baseline CSF tau and p-tau in predicting rates of whole-brain and regional medial temporal lobe atrophy in preclinical Alzheimer's disease has recently also been addressed in a longitudinal study with early Alzheimer's disease patients and cognitively healthy control individuals who were followed up over a period of 2–3 years [13▪]. Notably, cognitively intact individuals with CSF levels of total tau and p-tau in the upper tercile showed significantly increased atrophy rates when compared to healthy controls with levels in the lower two terciles [13▪].

On the basis of hypothesis that synergistic interactions between Aβ and tau pathology drive Alzheimer's disease-related neurodegeneration and neurometabolic dysfunction Pascoal *et al.* [14▪]

assessed 120 cognitively healthy individuals who had undergone CSF tap and [^{18}F]florbetapir amyloid PET at baseline in addition to an [^{18}F]FDG PET for glucose at baseline and at 24 months of follow-up. Voxel-based analysis revealed a decline in the [^{18}F]FDG standardized uptake value ratio (SUVR) in various limbic brain regions. Interestingly, this [^{18}F]FDG SUVR decline was significantly affected by the interaction between [^{18}F]florbetapir SUVR and CSF p-tau, while the main effects of [^{18}F]florbetapir and CSF p-tau were not significant, suggesting a synergism between Aβ and p-tau in driving metabolic decline in preclinical Alzheimer's disease [14▪].

The recent introduction of tau PET tracers has provided a valuable tool to investigate the spatial and temporal relationship between cerebral tau accumulation and established CSF measures of Alzheimer's disease pathology. In a first cross-sectional study in preclinical Alzheimer's disease, Gordon *et al.* [15▪▪] found a significant association between CSF Aβ42, but not total tau and p-tau, and elevated binding of the tau tracer [^{18}F]AV-1451 in the medial temporal lobes and adjacent cortices of cognitively intact individuals. Interestingly, a positive correlation between PET and CSF tau-related measures was observed when a combined analysis of both cognitively healthy and cognitively impaired individuals (CDR $\geq$0.5) was performed, which was mainly driven by the cognitively impaired individuals and associated with a more widespread uptake of the tau tracer in neocortical brain regions [15▪▪].

CORE CEREBROSPINAL FLUID BIOMARKER TRAJECTORIES AND AMYLOID IMAGING IN PRECLINICAL ALZHEIMER'S DISEASE

Sutphen *et al.* [16▪▪] characterized the within-person trajectories of various Alzheimer's disease CSF biomarkers in a longitudinal cohort of 169 cognitively intact middle-aged individuals who had undergone serial lumbar punctures and longitudinal clinical assessments as well as – in a subset of individuals – amyloid PET imaging. In support of the NIA-AA criteria suggesting an age-related transition between stage 1 (characterized by amyloid pathology only) and stage 2 (amyloidosis *and* presence of signs of neuronal injury), the authors found CSF levels of Aβ42 decreasing over time as early as during early middle age (45–54 years). These early changes were associated with significant elevations in the neuronal injury markers total tau and p-tau during mid middle age (55–64 years) and late middle age (65–74 years) [16▪▪]. As a major outcome, decreases in CSF Aβ42 were found even before detectable amyloid deposition on [^{11}C]PiB PET imaging in mid middle age [16▪▪]. Together with the observation that in some individuals [^{11}C]PiB binding was still below the threshold of positivity while CSF Aβ42 levels were already low, these results imply that changes in CSF Aβ42 may precede [^{11}C]PiB [16▪▪]. In support of these findings are recent cross-sectional data from a large familial Alzheimer's disease kindred of presymptomatic individuals carrying the Presenilin 1 E280A mutation in whom changes in CSF Aβ42 were detectable 20 years before the kindred's estimated mild cognitive impairment (MCI) diagnosis and 4 years prior to amyloid positivity on [^{18}F]florbetapir PET imaging [17].

The association between baseline CSF Aβ42 and longitudinal Aβ accumulation on amyloid PET has further been assessed in two recent longitudinal cohort studies. Palmqvist *et al.* [18▪] investigated whether abnormal Aβ accumulation can be detected by CSF analysis prior to amyloid PET in 437 nondemented individuals that included both cognitively intact individuals and patients with MCI. The authors found that individuals with abnormal CSF Aβ42, but normal [^{18}F]florbetapir PET at baseline ('CSF+/PET−'), showed a significantly accelerated rate of cerebral Aβ accumulation on follow-up amyloid PET which resembled the rate in individuals with both abnormal CSF and PET findings ('CSF+/PET+'). Interestingly, no 'CSF−/PET+' individuals were identified in this study, suggesting that CSF changes can indeed be detected prior to PET abnormalities [18▪]. Together with the observation that 'CSF+/PET−' individuals showed no memory decline and similar changes in hippocampal volume as 'CSF−/PET−' individuals over time, these results strongly indicate that CSF Aβ42 levels are altered in the earliest (preclinical) stages of Alzheimer's disease [18▪].

In another longitudinal study, Racine *et al.* [19] collected baseline CSF from 104 cognitively intact individuals (mean age 61.15 years) who were enriched with Alzheimer's disease risk factors (APOE ε4 genotype; positive family history of sporadic Alzheimer's disease). Linear mixed-effects regression analysis revealed that at baseline CSF Aβ42/Aβ40 ratio and various other ratios of CSF proteins to Aβ42, including total and p-tau, predicted longitudinal [^{11}C]PiB uptake in Alzheimer's disease-vulnerable brain regions over 2 years [19]. In contrast to the authors' initial hypothesis, no significant associations between baseline CSF ratios (including those with markers of neuronal injury such as total tau in the numerator) and slopes of episodic memory were detected suggesting that Alzheimer's disease-related preclinical cognitive decline may be too subtle in this relatively young cohort of cognitively healthy individuals [19].

In a serial CSF sampling study including 35 cognitively healthy individuals who were followed up longitudinally over a period of up to 3 years, Mattsson *et al.* [20▪] investigated whether baseline CSF levels of Aβ42 and p-tau predicted future amyloid positivity defined as declining CSF Aβ42 levels below an priori-defined threshold of 192 ng/l. Importantly, all participants included in this study had normal CSF Aβ42 levels at baseline. Although 10 out of 11 'decliners' showed baseline CSF Aβ42 levels in the lower tertile of the reference range (<225 ng/l), the majority of 'nondecliners' had CSF Aβ42 levels in the two upper tertiles [20▪]. Baseline p-tau levels also predicted future CSF Aβ42 decline; baseline CSF Aβ42 in the low normal range, however, turned out to be the strongest predictor of future amyloid positivity suggesting that in cognitively normal individuals a less stringent (i.e., higher) cutoff level may be considered [20▪].

The fact that both CSF Aβ42 and p-tau predicted future amyloidosis in this study might imply that the two pathologies are coupled early in Alzheimer's disease pathogenesis. In line with this notion, Gomar *et al.* [21▪] observed in a subset of cognitively normal individuals a strong temporal coincidence of CSF trajectories of Aβ42 and p-tau, which were anticorrelated in individuals with declining CSF Aβ42 levels over time.

In a cross-sectional preclinical Alzheimer's disease study with 38 cognitively normal individuals, Adamczuk *et al.* [22] assessed the diagnostic accuracy of CSF Aβ42 versus CSF Aβ42/total-tau, Aβ42/Aβ40 and Aβ42/Aβ38 in identifying amyloid-positivity on [^{18}F]flutemetamol PET imaging. Interestingly, when sensitivity and specificity were combined, the ratios to Aβ42 did not discriminate significantly better between amyloid-positive and amyloid-negative individuals than CSF Aβ42 alone. With a fixed specificity at 90 or 95%, however, Aβ42/total-tau showed the highest sensitivity, suggesting that a CSF-based diagnosis of preclinical Alzheimer's disease should include both biomarkers in cases when a high specificity is required (e.g., in therapeutic clinical trials) [22].

CORE CEREBROSPINAL FLUID BIOMARKERS AND PREDICTION OF COGNITIVE DECLINE

An important concern raised in preclinical Alzheimer's disease clinical trials lies in the challenge to identify patients who are likely to show greatest clinical progression if untreated. Soldan *et al.* [23▪▪] addressed this question in 222 cognitively intact individuals who underwent baseline lumbar puncture at middle age and cognitive follow-up over a time period of 11 years. Based on the NIA-AA criteria [3], the authors classified the individuals according to their CSF biomarker profiles at baseline into four hypothetical preclinical Alzheimer's disease groups: high Aβ42/low total or p-tau ('stage 0'), low Aβ42/low total or p-tau ('stage 1'), low Aβ42/high total or p-tau ('stage 2') and high Aβ42/high total or p-tau (referred to as suspected non-Alzheimer's disease pathology or 'SNAP'). By using an a priori-defined cognitive composite score Soldan *et al.* found significantly lower baseline scores and an increased cognitive decline over time only in the 'stage 2' group when compared to the other groups.

In line with these results are findings from a longitudinal cohort of middle-aged individuals in which the majority of individuals with cognitive decline during follow-up exhibited low Aβ42 and high tau/p-tau at baseline and follow-up [16▪▪].

Collectively, these results imply that the presence of tau pathology in CSF is required for cognitive decline in persons with preclinical Alzheimer's disease. An association between CSF tau, but not CSF Aβ, and cognitive deficits is further supported by data from a sample of cognitively intact individuals revealing a significant relationship between CSF tau and p-tau and longitudinal impairments on specific visuospatial episodic memory tasks [24].

In an alternative study, Edmonds *et al.* [25] analyzed 570 cognitively normal participants who were classified either based on the NIA-AA criteria or separately based on the number of positive CSF Alzheimer's disease biomarkers and on operationalized criteria defining 'subtle cognitive decline' in preclinical Alzheimer's disease. Interestingly, baseline analyses revealed a 2.5 times higher frequency of abnormal CSF tau levels than abnormal CSF Aβ in this sample; moreover, most of the individuals who were characterized by only one abnormal CSF biomarker at baseline and later progressed to MCI or Alzheimer's disease dementia turned out to be tau-positive [25].

In general, the relationship between tau pathology and cognitive decline does not exclude the possibility of tau-independent Aβ-related influences on cognition. In fact, in the cross-sectional study published by Wang *et al.* [11▪], abnormal CSF levels of Aβ42 and tau were not only associated with spatially distinct patterns of brain atrophy, but also with independent effects on cognitive performance in specific neuropsychological tasks.

CANDIDATE CEREBROSPINAL FLUID BIOMARKERS IN PRECLINICAL ALZHEIMER'S DISEASE

In the recent years, the involvement of neuroinflammatory responses in early Alzheimer's disease pathogenesis has received much attention by the

scientific community. Several markers have been studied with a special focus on YKL-40 (also known as chitinase 3-like 1 protein), a marker of glial inflammation. Two recent cross-sectional studies addressed the relationship between CSF YKL-40 and structural brain changes in cohorts including individuals with preclinical Alzheimer's disease. Alcolea *et al.* [26] found a strong correlation between CSF YKL-40 and the neurodegeneration markers total tau and p-tau in a combined sample of 80 cognitively normal controls and 27 MCI patients. Importantly, CSF YKL-40 levels were strongly correlated with cortical thinning in Alzheimer's disease-relevant brain regions associated with tau pathology and – similar to tau – were modulated by the CSF Aβ42 status suggesting that both tau-driven neurodegeneration and YKL-40-related inflammation affected brain structure in an amyloid-dependent manner [26]. Although these results imply a contribution of YKL-40-related processes and tau pathology to similar structural brain changes, Gispert *et al.* [27] recently reported an association of CSF YKL-40 and p-tau with grey matter atrophy in anatomically distinct brain regions in a cohort of MCI and mild Alzheimer's disease individuals as well as normal controls and individuals with preclinical Alzheimer's disease. In support of these findings, Sutphen *et al.* [16▪▪] observed in their longitudinal sample a consistent increase in CSF YKL-40 throughout middle age, which was accelerated by the presence of the APOE ε4 genotype, as were the changes in both amyloid and neuronal injury markers. A strong correlation between CSF YKL-40 and age as well as between YKL-40 and total tau was also observed in a large cross-sectional study including 266 middle-aged cognitively intact individuals [28]. Interestingly, significantly increased CSF YKL-40 levels were not only detected in individuals with preclinical Alzheimer's disease stages 2–3, but also in participants with SNAP, suggesting that markers of neuroinflammation may be of relevance in a wide range of neurodegenerative conditions including nonamyloid-related pathologies [28]. In the latter study, the authors additionally measured CSF sAPPβ levels and β-secretase activity, two candidate biomarkers involved in amyloid precursor protein (APP) processing, but found no significant differences between preclinical Alzheimer's disease stages 0, 1 and 2–3 [28].

Neuronal loss and synaptic injury are widely recognized as early correlates of Alzheimer's disease-related cognitive decline and clinical disease progression. Biomarkers of neuronal and synaptic loss may therefore be particularly useful as staging biomarkers in preclinical Alzheimer's disease. Among the candidate markers reflecting neuronal injury a special focus has recently been laid on the neuronal calcium-sensor protein visinin-like protein 1 (VILIP-1). Analysis of within-person trajectories of CSF biomarkers in middle-aged individuals included in the study published by Sutphen *et al.* [16▪▪] revealed significant increases in CSF VILIP-1 during mid and late middle age thus resembling the temporal biomarker changes observed for the neuronal injury markers total tau and p-tau in this study. Similar to CSF tau and p-tau, baseline CSF levels of VILIP-1 in the upper tercile were associated with significantly increased atrophy rates in cognitively normal participants in the longitudinal study published by Tarawneh *et al.* [13▪]. In early Alzheimer's disease patients, baseline CSF VILIP-1 levels moreover predicted regional and whole-brain atrophy at least as well as tau/p-tau [13▪].

In another cross-sectional and longitudinal observational study including 207 cognitively intact control individuals and 95 patients with symptomatic Alzheimer's disease Tarawneh investigated the diagnostic and prognostic utility of neurogranin, a candidate CSF marker of synaptic injury [29]. Although CSF neurogranin levels differentiated patients with early Alzheimer's disease from controls with a diagnostic accuracy comparable to the core CSF markers, CSF neurogranin also correlated with cerebral amyloid deposition on amyloid PET in individuals with preclinical Alzheimer's disease and predicted longitudinal cognitive decline in cognitively intact individuals [29]. In combination with the other CSF biomarkers of Alzheimer's disease, CSF neurogranin complemented the predictive ability for future cognitive decline, thus emphasizing the utility of its addition to the diagnostic panel in preclinical Alzheimer's disease [29].

CONCLUSION

Recent findings support the notion that elevated CSF tau/p-tau levels and/or Aβ/tau interactions are associated with neurodegeneration in preclinical Alzheimer's disease as revealed by Alzheimer's disease-characteristic changes on MRI and [^{18}F]FDG PET, which would be in line with the NIA-AA criteria [3]. However, a low concordance rate between CSF tau and imaging markers of neurodegeneration have been reported by some authors, and Aβ-mediated tau-independent effects on brain atrophy have been described, suggesting the need for further research in this field. Concerning the sequence of temporal biomarker changes, longitudinal data in cognitively intact individuals suggest that CSF Aβ42 is altered very early in preclinical Alzheimer's disease, even preceding changes on amyloid PET imaging [16▪▪,18▪]. The order of temporal changes of CSF Aβ

and tau, however, seems to be less clear as suggested by the NIA-AA criteria given the fact that a strong temporal coincidence of CSF Aβ trajectories tau trajectories has been observed by some authors. In the majority of studies, the presence of abnormal CSF tau/p-tau levels and/or combined Aβ and tau pathology were required for future cognitive deline, again in agreement with the proposed NIA-AA staging model [3]. Nevertheless, Aβ and tau may also exert independent effects on cognitive function as suggested by some authors. The search for novel CSF biomarkers has led to identification of several candidate biomarkers of neuronal and synaptic injury as well as neuroinflammation, which may complement CSF-based diagnostics in the different stages of preclinical Alzheimer's disease.

FUTURE DIRECTIONS

In addition to structural MRI and PET, a number of additional MR-based imaging techniques have recently been applied to study the functional consequences of CSF biomarker abnormalities in individuals with preclinical Alzheimer's disease and may further contribute to a better understanding of brain changes in the earliest stages of the disease [5▪▪,30,31].

To better predict cognitive decline in persons with preclinical Alzheimer's disease, the role of co-pathologies and the contribution of various lifestyle and risk factors will have to be better understood. In addition to vascular changes and vascular risk factors [32,33], the role of psychiatric comorbidities, such as anxiety and depression, and their association with preclinical Alzheimer's disease biomarkers and cognitive decline will have to be addressed further in longitudinal studies [34,35].

An under-researched topic in the biomarker field remains the discovery of novel markers reflecting beneficial clinical outcome and neuroprotection. As an example, CSF vascular endothelial growth factor (VEGF) has recently been associated with beneficial effects on longitudinal atrophy and cognitive function in the presence of abnormal Alzheimer's disease CSF biomarkers [36]. Other protective factors in preclinical Alzheimer's disease include cognitive reserve [23▪▪,37▪] and engagement in physical activity [38]. The exact contribution of these factors to longitudinal cognitive decline and their association with CSF biomarker changes in preclinical Alzheimer's disease will be an important aim of future research.

APOE ε4 represents the major genetic risk factor for sporadic Alzheimer's disease. In the study published by Sutphen *et al.* [16▪▪], the APOE ε4 genotype was associated with more pronounced longitudinal changes of Alzheimer's disease-related biomarker trajectories in cognitively normal individuals during middle age in whom it modified CSF Aβ42 levels in allele dose-dependent manner. Whether Alzheimer's disease biomarkers, including markers of cerebral amyloid plaque deposition, and APOE ε4 act independently or interact with each other to influence longitudinal cognitive decline is still a matter of debate. Although Soldan *et al.* [23▪▪] reported an overrepresentation of APOE ε4 carriers in individuals with stage 2 preclinical Alzheimer's disease, the APOE ε4 genotype did not significantly modify the rate of cognitive decline in this study. These results are in contrast to the findings obtained from several recent preclinical Alzheimer's disease studies suggesting an interaction between Aβ positivity, as determined by amyloid PET imaging, and APOE ε4 genotype on the progression of future cognitive symptoms [39–43]. Taken together, additional longitudinal studies with genetic and CSF biomarker data from larger sample sizes will be necessary to delineate the role of APOE ε4 and its interaction with core CSF Alzheimer's disease biomarkers in longitudinal cognitive decline.

Acknowledgements

None.

Financial support and sponsorship

L.K. was supported by the Velux Foundation (Project No. 993).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Scheltens P, Blennow K, Breteler MM, *et al.* Alzheimer's disease. Lancet 2016; 388:505–517.
2. Villemagne VL, Burnham S, Bourgeat P, *et al.* Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol 2013; 12:357–367.
3. Sperling RA, Aisen PS, Beckett LA, *et al.* Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7:280–292.
4. Dubois B, Feldman HH, Jacova C, *et al.* Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014; 13:614–629.
5. ▪▪ Dubois B, Hampel H, Feldman HH, *et al.* Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. Alzheimers Dement 2016; 12:292–323.

This review article provides detailed recommendations and a very comprehensive overview of the key research questions in preclinical Alzheimer's disease.

6. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 2016; 8:595–608.
7. Jack CR Jr, Knopman DS, Jagust WJ, *et al.* Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010; 9:119–128.

8. Jack CR Jr, Knopman DS, Jagust WJ, *et al.* Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013; 12:207–216.

9. Jagust W. Is amyloid-beta harmful to the brain? Insights from human imaging studies. Brain 2016; 139 (Pt 1):23–30.

10. ■ Vos SJ, Gordon BA, Su Y, *et al.* NIA-AA staging of preclinical Alzheimer disease: discordance and concordance of CSF and imaging biomarkers. Neurobiol Aging 2016; 44:1–8.

This article reports a surprisingly low concordance rate between CSF and imaging markers of neurodegeneration, thus questioning the assumption that these markers may be used as if they were interchangeable.

11. ■ Wang L, Benzinger TL, Hassenstab J, *et al.* Spatially distinct atrophy is linked to beta-amyloid and tau in preclinical Alzheimer disease. Neurology 2015; 84:1254–1260.

In this study, CSF Aβ and tau are associated with distinct patterns of brain atrophy.

12. ■ Fortea J, Vilaplana E, Alcolea D, *et al.* Cerebrospinal fluid beta-amyloid and phospho-tau biomarker interactions affecting brain structure in preclinical Alzheimer disease. Ann Neurol 2014; 76:223–230.

This cross-sectional study describes a significant interaction between CSF Aβ and p-tau affecting brain structure.

13. ■ Tarawneh R, Head D, Allison S, *et al.* Cerebrospinal fluid markers of neurodegeneration and rates of brain atrophy in early Alzheimer disease. JAMA Neurol 2015; 72:656–665.

This longitudinal study in cognitively intact persons shows that CSF levels of tau/p-tau in the upper range are associated with increased atrophy rates over time.

14. ■ Pascoal TA, Mathotaarachchi S, Mohades S, *et al.* Amyloid-beta and hyperphosphorylated tau synergy drives metabolic decline in preclinical Alzheimer's disease. Mol Psychiatry 2016. [Epub ahead of print]

The authors report a synergistic interaction between Aβ accumulation on amyloid PET imaging and CSF p-tau in driving neurometabolic dysfunction in preclinical Alzheimer's disease.

15. ■■ Gordon BA, Friedrichsen K, Brier M, *et al.* The relationship between cerebrospinal fluid markers of Alzheimer pathology and positron emission tomography tau imaging. Brain 2016; 139:2249–2260.

The first study investigating the relationship between core CSF biomarkers and tau PET imaging.

16. ■■ Sutphen CL, Jasielec MS, Shah AR, *et al.* Longitudinal cerebrospinal fluid biomarker changes in preclinical Alzheimer disease during middle age. JAMA Neurol 2015; 72:1029–1042.

This longitudinal study characterizes the within-person trajectories of various CSF biomarkers and their association with cerebral amyloid deposition and cognition in preclinical Alzheimer's disease during middle age.

17. Fleisher AS, Chen K, Quiroz YT, *et al.* Associations between biomarkers and age in the presenilin 1 E280A autosomal dominant Alzheimer disease kindred: a cross-sectional study. JAMA Neurol 2015; 72:316–324.

18. ■ Palmqvist S, Mattsson N, Hansson O.; Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid analysis detects cerebral amyloid-beta accumulation earlier than positron emission tomography. Brain 2016; 139 (Pt 4):1226–1236.

This longitudinal cohort study suggests that changes in CSF Aβ42 precede changes on amyloid PET imaging.

19. Racine AM, Koscik RL, Nicholas CR, *et al.* Cerebrospinal fluid ratios with Abeta42 predict preclinical brain beta-amyloid accumulation. Alzheimers Dement (Amst) 2016; 2:27–38.

20. ■ Mattsson N, Insel PS, Donohue M, *et al.* Predicting reduction of cerebrospinal fluid beta-amyloid 42 in cognitively healthy controls. JAMA Neurol 2015; 72:554–560.

This longitudinal study with serial CSF sampling over time suggests that baseline CSF Aβ42 in the low normal range is a strong predictor of future amyloid positivity; this implies that in cognitively normal individuals less stringent (i.e., higher) cutoff levels may be considered.

21. ■ Gomar JJ, Conejero-Goldberg C, Davies P, Goldberg TE.; Alzheimer's Disease Neuroimaging Initiative. Anti-correlated cerebrospinal fluid biomarker trajectories in preclinical Alzheimer's disease. J Alzheimers Dis 2016; 51:1085–1097.

This longitudinal study describes a close relationship between CSF Aβ42 and p-tau trajectories already in the very early stages of preclinical Alzheimer's disease.

22. Adamczuk K, Schaeverbeke J, Vanderstichele HM, *et al.* Diagnostic value of cerebrospinal fluid Abeta ratios in preclinical Alzheimer's disease. Alzheimers Res Ther 2015; 7:75.

23. ■■ Soldan A, Pettigrew C, Cai Q, *et al.* Hypothetical preclinical alzheimer disease groups and longitudinal cognitive change. JAMA Neurol 2016; 73:698–705.

In this study, the authors classified cognitively healthy persons according to the NIA-AA criteria into four hypothetical groups based on their CSF core biomarker profile. Cognitive decline during follow-up was evident only in individuals with abnormal CSF levels of both Aβ42 and tau/p-tau at baseline.

24. Pettigrew C, Soldan A, Moghekar A, *et al.* Relationship between cerebrospinal fluid biomarkers of Alzheimer's disease and cognition in cognitively normal older adults. Neuropsychologia 2015; 78:63–72.

25. Edmonds EC, Delano-Wood L, Galasko DR, *et al.*; Alzheimer's Disease Neuroimaging Initiative. Subtle cognitive decline and biomarker staging in preclinical Alzheimer's disease. J Alzheimers Dis 2015; 47:231–242.

26. Alcolea D, Vilaplana E, Pegueroles J, *et al.* Relationship between cortical thickness and cerebrospinal fluid YKL-40 in predementia stages of Alzheimer's disease. Neurobiol Aging 2015; 36:2018–2023.

27. Gispert JD, Monte GC, Falcon C, *et al.* CSF YKL-40 and pTau181 are related to different cerebral morphometric patterns in early AD. Neurobiol Aging 2016; 38:47–55.

28. Alcolea D, Martinez-Lage P, Sanchez-Juan P, *et al.* Amyloid precursor protein metabolism and inflammation markers in preclinical Alzheimer disease. Neurology 2015; 85:626–633.

29. Tarawneh R, D'Angelo G, Crimmins D, *et al.* Diagnostic and prognostic utility of the synaptic marker neurogranin in Alzheimer disease. JAMA Neurol 2016; 73:561–571.

30. Gordon BA, Zacks JM, Blazey T, *et al.* Task-evoked fMRI changes in attention networks are associated with preclinical Alzheimer's disease biomarkers. Neurobiol Aging 2015; 36:1771–1779.

31. Voevodskaya O, Sundgren PC, Strandberg O, *et al.* Myo-inositol changes precede amyloid pathology and relate to APOE genotype in Alzheimer disease. Neurology 2016; 86:1754–1761.

32. Nation DA, Edmonds EC, Bangen KJ, *et al.* Pulse pressure in relation to tau-mediated neurodegeneration, cerebral amyloidosis, and progression to dementia in very old adults. JAMA Neurol 2015; 72:546–553.

33. Oikonomidi A, Lewczuk P, Kornhuber J, *et al.* Homocysteine metabolism is associated with cerebrospinal fluid levels of soluble amyloid precursor protein and amyloid beta. J Neurochem 2016; 139:324–332.

34. Pietrzak RH, Lim YY, Neumeister A, *et al.* Amyloid-beta, anxiety, and cognitive decline in preclinical Alzheimer disease: a multicenter, prospective cohort study. JAMA Psychiatry 2015; 72:284–291.

35. Donovan NJ, Hsu DC, Dagley AS, *et al.* Depressive symptoms and biomarkers of Alzheimer's disease in cognitively normal older adults. J Alzheimers Dis 2015; 46:63–73.

36. Hohman TJ, Bell SP, Jefferson AL.; Alzheimer's Disease Neuroimaging Initiative. The role of vascular endothelial growth factor in neurodegeneration and cognitive decline: exploring interactions with biomarkers of Alzheimer disease. JAMA Neurol 2015; 72:520–529.

37. ■ Vemuri P, Lesnick TG, Przybelski SA, *et al.* Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. Brain 2015; 138 (Pt 3):761–771.

This study suggests an additive effect of vascular and amyloid pathologies on longitudinal cognitive decline in cognitively healthy elderly individuals.

38. Okonkwo OC, Schultz SA, Oh JM, *et al.* Physical activity attenuates age-related biomarker alterations in preclinical AD. Neurology 2014; 83:1753–1760.

39. Lim YY, Villemagne VL, Laws SM, *et al.* APOE and BDNF polymorphisms moderate amyloid beta-related cognitive decline in preclinical Alzheimer's disease. Mol Psychiatry 2015; 20:1322–1328.

40. Thai C, Lim YY, Villemagne VL, *et al.* Amyloid-related memory decline in preclinical Alzheimer's disease is dependent on APOE epsilon4 and is detectable over 18-months. PLoS One 2015; 10:e0139082.

41. Lim YY, Villemagne VL, Pietrzak RH, *et al.* APOE epsilon4 moderates amyloid-related memory decline in preclinical Alzheimer's disease. Neurobiol Aging 2015; 36:1239–1244.

42. Mormino EC, Betensky RA, Hedden T, *et al.* Amyloid and APOE epsilon4 interact to influence short-term decline in preclinical Alzheimer disease. Neurology 2014; 82:1760–1767.

43. Pietrzak RH, Lim YY, Ames D, *et al.* Trajectories of memory decline in preclinical Alzheimer's disease: results from the Australian Imaging, Biomarkers and Lifestyle Flagship Study of ageing. Neurobiol Aging 2015; 36:1231–1238.